Message

From: Subramaniam, Ravi [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=E738F9D27062486E9047184B867FD968-SUBRAMANIAM, RAVI]
Sent: 3/6/2016 4:50:59 AM
To: Gary Ginsberg [Gary.Ginsberg@po.state.ct.us]; gary.ginsberg@ct.gov
Subject: bottom up discussion
Attachments: RTP-S-14-00253.a.pdf

Hi Gary:

I am attaching our letter to the editor (which you have) with a couple of sentences highlighted. We can focus on these sentences and the figure in the letter to the editor when we talk on Tuesday. The DNA repair issue you touched upon has direct implication on potentially different slopes and/or curvatures in the endogenous and exogenous regions. I think you were saying the same thing even if coming at it a bit differently.

Also, here is a paragraph that we eventually left out of the letter thinking it might distract from the main argument.

> Even if the dose-response were linear below a typical endogenous internal concentration, there are numerous assumptions made by the approach (such as that the appropriate internal moiety has been identified, that the site of initial action has been identified, that the estimates of internal dose are reasonably accurate, and that the range of human variability in factors affecting PBPK or pharmacodynamics have been identified). The authors note the reasonably certainty in estimates of population background rates for some cancers. However, given significant uncertainty regarding the range of assumptions going into the "bottom up" approach, the approach is at best a "what if" estimate and is not demonstrably a procedure for establishing an upper bound on estimates of risk derived by other means.

--Ravi.

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